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HISTORICAL PERSPECTIVE

Of unglazed pottery and glomerular sieving

To the student interested in the evolution of ideas and concepts of renal function, the contributions of William Bowman and Carl Ludwig are generally viewed as fundamental. In his classic paper of 1842 [1], Bowman described in remarkable detail the structure of the renal corpuscle (of Malpighi), and suggested that the arrangement of glomerular capillaries therein was ideally suited to the task of separating water from plasma. He reasoned that all urinary constituents other than water were added to the watery filtrate by the epithelial cells of the tubules by a process akin to secretion, the water merely serving to carry the secreted substances along the tubules into the bladder. Ludwig, whose knowledge of physical chemistry was unusually advanced for his time, soon challenged the interpretations of Bowman, arguing instead that the initial event in the process of urine formation is more likely to involve the separation from plasma of a protein-free ultrafiltrate by the walls of the glomerular capillaries [2]. His insight was by no means confined to this important statement, for he went on to suggest that as ultrafiltrate flows along the tubule, its volume is reduced and its constituents concentrated (more or less proportionally) by a reabsorptive process, the driving force for which is derived from the chemical energy of the raised protein concentration of the peritubular capillary blood plasma (a process he called "endosmosis").

These scientific contributions of the 1840's are generally held by renal physiologists to constitute a cornerstone in the development of the "modern view" of renal physiology in general, and of our understanding of glomerular filtration in particular. Nevertheless, the notion that the kidney might be likened to a sieve was appreciated prior to the time of Bowman and Ludwig, and is probably among the oldest of views concerning the nature of urine formation. For example, in his major work, *De Viscerum Structura Exercitatio Anatomica* [3,4], published in 1666, Marcello Malpighi wrote: "The ancients conceived of the kidney as a sieve providing a means for separating the urine." Indeed, this was a view which his own observations led him to endorse. While we cannot be at all sure, it might be imagined that this revelation reflected reasoning by simple analogy, for a clear non-opaque urine formed by the kidneys through which coursed the dark and highly opaque blood was in many respects similar to the process employed by the ancients of using vessels of unglazed pottery as a means for separating clear, sparkling wine from a ferment clouded with sediment.

It has come to our attention that the idea that the kidney functions as a sieve received considerable attention in Japan in the late part of the 18th century, and that by 1805, the results of some early experimental studies relating to the mechanisms of urine formation had been recorded. The purpose of this brief essay is to draw attention to these contributions made by Japanese physiologists nearly a half-century before the writings of Bowman and Ludwig.[1]

Oranda-Iji-Mondo and Oranda-Iwa

The introduction of European medicine into Japan by Jesuit priests from Spain and Portugal occurred in the middle of the 16th century. For the next 250 years, however, Japan was essentially isolated, both politically and culturally, from Europe except for limited trading with the Dutch East India Company. A Dutch book of anatomy was first translated into Japanese by Gempaku Sugita and Ryotaku Maeno in 1774, followed by nearly a century of verbatim translations of this work. One exception was the treatise *Oranda-Iji-Mondo* (Discussion of Dutch Medicine), written in 1795 by the son of Gempaku Sugita, in which is found the first recorded Japanese attempts at structure-function correlations relating to the kidney. Thus, we find the following passage (translated from [7] by one of us [I.I.]):

> These two thick trunk vessels reside on the dorsal wall of the abdomen, parallel with the spinal bones and connect with the heart. There are branch vessels running to the kidneys on both sides from these trunk vessels. Of the blood, which comes into the kidneys through these vessels, salty water is separated and filtered in the kidney into clean urine. . . .

[1] Brief translations and commentaries in English dealing with these early Japanese contributions have appeared previously [5,6]. Since these sources are not likely to be familiar to the majority of non-Japanese renal physiologists, the aim of the present report is to document more fully these historical contributions and make them available to the interested and specialized readership of this journal.

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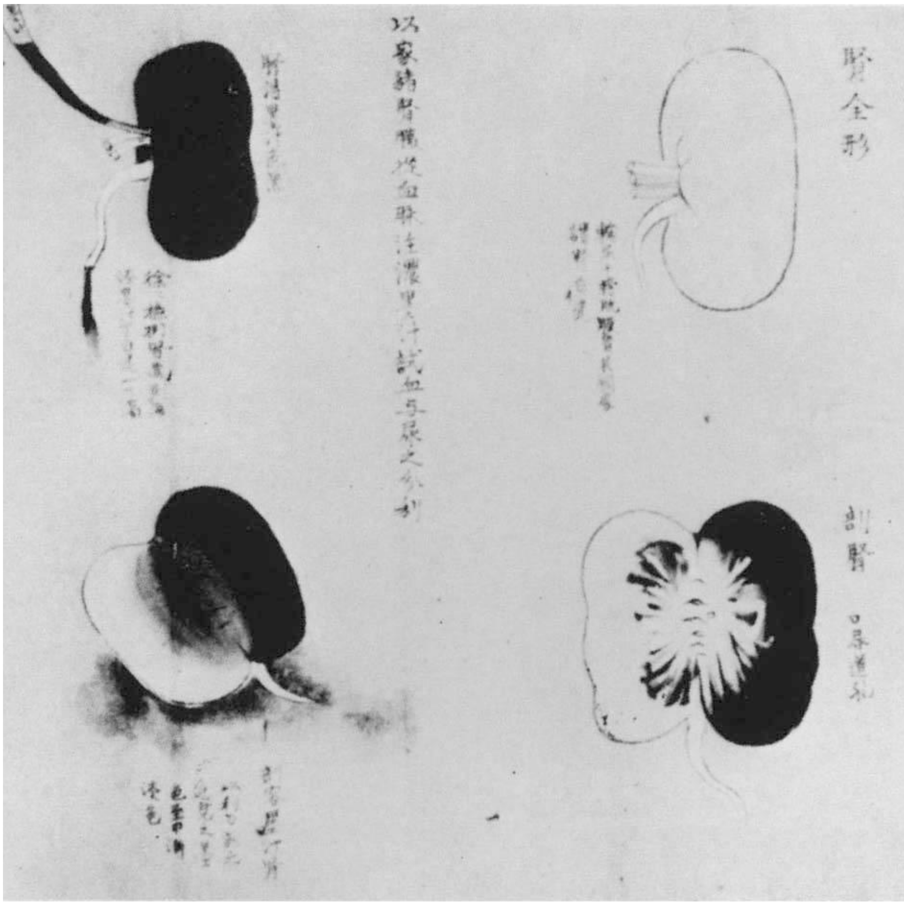

Fig. 1. *Fuseya's sketches of a pig's kidney* (right upper and lower) *and experimental findings with India ink* (left upper and lower). Following injection of India ink into the renal artery, relatively unstained fluid courses through the ureter, and in the sagittal section the black part of the ink is seen to remain in the kidney, darkest in the cortex. The Japanese text under the left upper figure states that the urine emerging from the cut end of the ureter was relatively unstained, although in this black and white sketch, the urine appears quite dark, simply to illustrate this fluid phase.

The kidney plays a role in separating water from the blood, as a certain kind of ductile organ. In this regard, the kidney is analogous to a water-filtering stone.

The daily food and drink is altered to form the blood running through the body. But we could not live if these [ingested substances] were allowed to accumulate. The kidneys filter the excess water in the following manner: When we allow Sumi[2] to remain overnight in an unglazed earthen pot, a clear watery filtrate comes through the wall of the pot, with the black material remaining inside the pot. Similarly, the kidneys filter and separate blood to form the urine, which in turn is expelled from the bladder. The remaining blood again courses through the body.

[2] India ink.

It is important to appreciate that at the time *Oranda-Iji-Mondo* was written, Japanese medicine was still based almost entirely on Chinese teachings. According to prevailing Chinese precepts [8], the role of the kidney was believed to be concerned with reproduction. Indeed, a reduction in sexual activity was ascribed to "lack of kidney". This fundamental discrepancy between Chinese precepts and the more plausible view of renal function contained in *Oranda-Iji-Mondo* triggered a remarkable series of experiments by Kimpan Fuseya, a physician who practiced in the Kansai district of Japan. In 1805, in a small woodcut publication of a book entitled *Oranda-Iwa* (A Story of Medicine in Holland), Fuseya described his experiments involving the injection of India ink into the renal artery of pigs and other animals. Since the black ink did not escape into the bladder but clear

Fig. 2. *The experiment of blue dye in Kansei-no-Fujin-Kaibozu.* In this reproduction of the original color picture by Oya, Indigo blue dye was injected into the substance of the left kidney of a recently deceased human female, the blue dye coursing through the left ureter and filling the bladder.

fluid did, he concluded that urine is filtered from the blood by an action of the kidneys. Fuseya [8] wrote:

> It is clear that there are three tubes to and from the kidney. First is the artery through which blood comes into the kidney, second is a vessel through which blood leaves the kidney, and third is a tube through which sieved salty water enters the bladder. . . . The experimental method by which I proved the theory [of filtration] using animals is as follows: After shaking and compressing the bladder and expelling the urine from it, I injected Sumi through a cannula in the renal artery. When sufficient quantity of Sumi seemed to have been introduced, I removed the cannula and pressed the kidney with the hand. I found that the black part of the ink remained in the kidney (Fig. 1) . . . while non-black clear water could be seen flowing through the [ureteral] tube, filling and expanding the bladder. When the bladder was pressed, the water emerged from the urethra of the penis. This finding was shown to be reproducible following many experiments in the same and different animals, using identical methods. It can be clearly demonstrated that the black part of Sumi is analogous to blood, and the clear water to the urine. Both the outside and the inside of the kidney after this experiment became black. The black coloration inside the kidney can be seen after sectioning. (Fig. 1).

Inasmuch as the fluid emerging from the kidney was sufficient in quantity to fill the initially empty bladder, it can be presumed that the fluid represented new filtrate formed in response to the infusion. Therefore, the experiment quite clearly demonstrates that the kidney can separate the relatively large and insoluble carbon particles in the ink from its watery base. Less clear are the results of an experiment of Shosai Oya and Bunken Kagami, physicians working in association with Fuseya. In their atlas *Kansei-no-Fujin-Kaibozu* (Atlas of Female Anatomy in the Era of Kansei) which appeared in 1800, they reported infusing "Ai", a soluble blue dye,[3] into the substance of the left kidney of a human female criminal who had recently been executed. As shown in Fig. 2, taken from [9], the blue dye appeared in the ureter and filled the urinary bladder. Assuming that the dye traversed glomeruli before appearing in the urine

[3] Ai, a soluble blue extract of indigo leaves (Indigo blue) is probably the oldest known coloring material. Its molecular weight has been determined to be 262, and therefore sufficiently small to penetrate the walls of glomerular capillaries without restriction.

(rather than entering the urine from tubules damaged by the cannula), their findings suggested to them that small, soluble molecules pass readily through the kidney filter.

One cannot fail to be impressed by the way these early Japanese physicians, using primitive experimental techniques and working in almost total academic isolation from their European contemporaries, attempted to elucidate the role of the kidney in urine formation. The experimental demonstration that the kidney functions as a sieve preceded the work of Bowman and Ludwig by nearly a half-century. Judging from their observations with India ink in which the large insoluble particles of this dye remained within the kidney, while the smaller soluble molecules of Indigo blue appeared in the bladder urine, they clearly appreciated the separatory ability of the kidney for solutes of differing size. Of interest is the fact that they arrived at their conclusions despite a lack of awareness of the fine structure of the glomerulus or of its anatomical relation to the renal tubule, whereas such awareness on the part of Bowman and Ludwig was precisely the stimulus that led to their speculations about the filtration process.

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